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Case Report

A Discounted Interaction, Divalproex sodium and Topiramate Induced Hyperammonemic Encephalopathy – A Case Report

P. Brittany Vickery[1]*, Victoria L. Do[2] and Carrie L. Griffiths[1]

[1]*Department of Pharmacy, Wingate University School of Pharmacy, USA*
[2]*Saint Vincent Hospital Pharmacy Department, MCPHS University School of Pharmacy, USA*

***Corresponding author**
P. Brittany Vickery, Assistant Professor of Pharmacy, Wingate University School of Pharmacy ,220 Fifth Avenue East , Hendersonville, NC 28792, USA, Tel: 828-697-0105 ext 24; Fax: 828-697-2065; Email: b.vickery@wingate.edu

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Abstract

An interaction between divalproex sodium and topiramate may induce hyperammonemic encephalopathy, a well-documented, but seemingly overlooked or minimized adverse drug interaction. This case report highlights a 54 year old Caucasian female who presented with sedation, mental status changes, and a history of repeated hospitalizations of similar presentation along with hyperammonemia. The patient had a significant past medical history for seizure and psychiatric conditions. A serious drug-drug interaction between divalproex and topiramate was overlooked in this patient, potentially causing hyperammonemic encephalopathy. Clinicians must work to be vigilant in monitoring medication lists for drug interactions, especially when polypharmacy is involved, in treating multiple disease states, or if the patient has numerous consulting specialists.

INTRODUCTION

There are over 2 million serious adverse drug reactions yearly which have been estimated to lead to more than 106,000 deaths annually [1]. Drug interactions represent 3% to 5% of preventable adverse drug reactions [1]. When polypharmacy is involved, patients are utilizing both specialists and primary care providers for treatment, drug interactions may be overlooked which can lead to negative consequences [2].

Divalproex sodium is comprised of sodium valproate and valproic acid. It dissociates into valproate ions in the gastrointestinal tract and the mechanism of action is thought to be related to increased brain concentrations of gamma-aminobutyric acid (GABA). Divalproex sodium is an antiepileptic drug indicated for treatment of mania or mixed episodes associated with bipolar disorder, complex partial seizures and simple and complex absence seizures, adjunctive therapy with multiple types of seizure, and migraine headache prophylaxis [3].

Topiramate is an antiepileptic drug indicated for partial onset or primary generalized tonic-clonic seizures, adjunctive therapy for epilepsy, and prophylaxis of migraine headaches. While the exact mechanism is unknown, efficacy is suggested to be due to its blocking activity of voltage dependent sodium channels, potentiation of GABA activity, antagonism of the AMPA/kainite subtype of the glutamate receptor, and the inhibition of carbonic anhydrase enzyme [4].

The interaction between divalproex sodium and topiramate is considered to be a moderate risk drug interaction which is not thought to be due to a pharmacokinetic reaction [3]. Topiramate may enhance the adverse and toxic effects of divalproex which lead to an increased risk of hyperammonemia, encephalopathy, hepatic failure, and hypothermia. Hyperammonemic encephalopathy can occur with or without hepatic failure [3, 5]. Other symptoms of hyperammonemic encephalopathy include altered mental status, confusion, lethargy, depression or anxiety, seizures, insomnia, and changes in behavior and personality [7]. Additionally case reports of valproic acid (VPA) induced encephalopathy exist in the presence of normal VPA levels, ammonia levels, or both [6-8].

This case report will concentrate on the potentially fatal consequences of the divalproex and topiramate interaction induced hyperammonemic encephalopathy. Reportedly, just over 50% of patients receiving valproic acid have asymptomatic hyperammonemia [9]. In some instances, topiramate induced hyperammonemia was dose related, worsening as the dose increased. However, no specific ammonia level monitoring information is included in the package inserts of divalproex sodium or topiramate [3,4]. Specific warnings related to both symptomatic and asymptomatic elevations of ammonia are present in the divalproex sodium package insert. Once hyperammonemia or mental status changes present, the patient requires close monitoring of status and plasma ammonia levels. If the elevation persists, discontinuation of divalproex sodium, topiramate, or both should be considered [3]. Despite the common use of divalproex sodium for both psychiatric and neurologic disorders, literature is sparse that has been published reviewing divalproex and topiramate induced hyperammonemic encephalopathy.

CASE PRESENTATION

A 54 year old Caucasian female with a history of schizoaffective disorder and a long history of seizure disorder presented to the emergency department from a non-hospital facility due to increasing reports of confusion. According to the staff at the group home, the patient had not been performing normal activities, showed decreased hygiene and personal care, had not been eating well, and has become increasingly agitated over the past few days. Two weeks prior to coming to the emergency department, the patient was discharged from another medical center after being evaluated in their emergency department with similar symptoms. During her ED evaluation, the electrocardiogram (EKG) showed normal sinus rhythm, CT scan of the head without contrast showed no evidence of acute intracranial process, and magnetic resonance imaging (MRI) scan of the brain without contrast showed no acute intracranial abnormalities. The patient has a past medical history (PMH) of grand mal seizures since the age of 2 years old, complex partial seizures, schizoaffective disorder, and unconfirmed cirrhosis which are pertinent to this case. Additional PMH can be found in (Table 1). The patient also had a significant history of multiple hospitalizations for altered mental status and multiple modifications of divalproex sodium ER and topiramate doses (Table 2). Upon admissions, the patient was taking multiple home medications (Table 3) and the medications of special pertinence to this case include: divalproex sodium ER 250 mg tablets 3 tablets by mouth every 12 hours, lacosamide 200 mg tablets 1 tablet by mouth every 12 hours, lactulose 20 gram/30 mL solution 30 mL by mouth 3 times a day, levetiracetam 500 mg tablet 1 tablet by mouth twice daily, oxcarbazepine 300 mg tablet 1.5 tablet by mouth twice daily, rifaximin 550 mg tablet 1 tablet by mouth every 12 hours, and topiramate 100 mg tablet 1 tablet by mouth twice daily. Pertinent labs include ammonia 124 umol/L and valproic acid level of 104 ug/mL (Table 4). This patient was hospitalized for a total of 12 days prior to discharge.

Upon admission, the patient was simply diagnosed with encephalopathy, which was thought to be the cause of the patient's continuous confusion and altered mental status due to slightly elevated blood levels of valproic acid. The patient's ammonia levels continuously increased until day 3 of admission even with continuation of the patient's home doses of lactulose and rifaximin. The patient was treated by increasing lactulose to 30 gram solution (45 mL) by mouth every 6 hours and continuing rifaximin 550 mg tablet 1 tablet by mouth every 12 hours for hyperammonemia. Within the first 48 hours of admission, pharmacy reviewed the patient's home medication list and discovered a drug interaction between divalproex and topiramate which was suspected to have caused the patient's hyperammonemic encephalopathy. Extended release valproic acid was eventually held and not given to the patient beginning on day three of hospitalization. After a review of past hospitalization notes, it was found that when physicians made an attempt to stabilize the patient's seizures and schizoaffective disorder by altering the doses of divalproex and/or topiramate, these alterations, which were typically increases of the doses, resulted in a hospitalization due to altered mental status. One physician even acknowledged the drug interaction between divalproex and topiramate causing hyperammonemic encephalopathy, but stated that the patient's neurologist strongly discouraged changing any medications that were prescribed to treat seizure disorder, even though the patient was receiving five antiepileptic medications. The neurologist made it clear that treatment of the patient's seizures would stop if these changes were made and that the patient would then have to find a new specialist. This was eventually resolved when the hospital's consulting psychiatrist contacted the neurologist and explained in detail, the drug interaction and resulting acute mental status changes, confusion, and sedation secondary to the hyperammonemia. The patient and this occurrence scored a 7 on the Naranjo Adverse Drug Reaction Probability Scale making this event a probable adverse drug reaction [10]. Prior to discharge, the patient was slowly tapered off of topiramate and divalproex was discontinued. The patient continued her current regimen of oxcarbazepine, levetiracetam,

Table 1: Complete Past Medical History.

Grand mal seizures since 2 years of age	GERD
Complex partial seizures	Obesity
Schizoaffective disorder	Hypertension
Depression	Asthma/COPD
Hyponatremia	Hyperlipidemia
Cirrhosis - unconfirmed	Hypothyroidism
Metabolic encephalopathy	

Abbreviations: GERD: Gastroesophageal Reflux Disease; COPD: Chronic Obstructive Pulmonary Disease

Table 2: Past Hospitalizations and dose adjustments of medications.

Date	Divalproex Sodium ER	Topiramate	Hospitalization
01/2005	250 mg daily	200 mg daily	Seizure
07/2012	250 mg daily	200 mg BID	AMS/ Psychiatric Hospitalization
09/2012	500 mg TID	200 mg BID	3 seizures in one day
04/2013	500 mg Q12H	100 mg AM 200 mg PM	Psychiatric Hospitalization
12/2013	500 mg at night	100 mg AM	Seizures
7/2014	750 mg BID	100 mg daily	AMS x 2

Abbreviations: AMS: Altered Mental Status

Table 3: Medications at time of admission and discharge.

Admission Medication	Indication	Discharge Medication
Calcium carbonate 500 mg Take 2 tablets PO daily	GERD	Yes
Carvedilol 3.125 mg Take 1 tablet PO Q12H	Hypertension	Yes
Cholecalciferol 1,000 IU Take 1 tablet PO daily	Supplement	Yes
Folic Acid 1 mg Take 1 tablet PO daily	Supplement	Yes
Clopidogrel 75 mg Take 1 tablet PO daily	Heart Protection	Yes
Fluticasone HFA 220 mcg Inhale 2 puffs Q12H. Rinse mouth after use.	Asthma/COPD	Yes
Lorazepam 0.5 mg Take 1 tablet by mouth TID	Anxiety	Yes
Metaxalone 800 mg Take ½ tablet PO Q12H PRN	Muscle Spasms	Yes
Quetiapine 200 mg Take 2 tablets PO daily QHS	Schizoaffective Disorder	Yes
Chlorpromazine 25 mg Take ½ tablet PO daily at 1PM	Schizoaffective Disorder	Yes
Citalopram 20 mg Take 1 tablet PO daily	Depression	Yes
Levothyroxine 50 mcg Take 1 tablet PO daily	Hypothyroidism	Yes
Divalproex Sodium 250 mg Take 3 tablets PO Q12H	Complex partial seizures	No
Topiramate 100 mg Take 1 tablet PO BID	Primary generalized tonic-clonic seizures	No
Oxcarbazepine 300 mg Take ½ tablet PO BID	Partial seizures	Yes
Lacosamide 200 mg Take 1 tablet PO Q12H	Partial seizures	Yes
Levetiracetam 500 mg Take 1 tablet PO BID	Partial seizures/primary generalized tonic-clonic seizures	Yes
Rifaximin 550 mg Take 1 tablet by mouth Q12H	Elevated Ammonia	Yes
Lactulose 20gram/30mL Solution Take 30 mL by mouth TID	Elevated Ammonia	Yes

Abbreviations: GERD: Gastroesophageal Reflux Disease; COPD: Chronic Obstructive Pulmonary Disease

and lacosamide (Table 3). No additional antiepileptic drugs were added and current antiepileptic drug doses were not altered at this time. Reportedly, the patient's seizures had been previously controlled on the five drug regimen for 2 years. She was also referred to a gastrointestinal specialist for livery biopsy to confirm or rule out suspected cirrhosis. After discharge from the hospital, the patient went to a skilled nursing home. The patient was not admitted again to this particular facility for any seizures or acute mental status changes for at least three months following this event.

Table 4: Pertinent Lab Values.

Test	Reference Range	Result
Sodium	136-145 mmol/L	140 mmol/L
Potassium	3.5-5.1 mmol/L	3.7 mmol/L
AST	15-41 IU/L	14 IU/L
ALT	14-54 IU/L	8 IU/L
ALK Phosphatase	34-104 IU/L	45 IU/L
Albumin	3.5-5.2 g/dL	3.3 g/dL
BUN	6-20 mg/dL	17 mg/dL
Total Bilirubin	0.3-1.2 mg/dL	0.3 mg/dL
Creatinine	0.60-1.10 mg/dL	0.59 mg/dL
Ammonia	9-35 umol/L	124 umol/L
WBC	4.0-9.2 K/uL	3.7 K/uL
RBC	3.90-5.10 M/uL	3.66 M/uL
Platelet	150-450 K/uL	137 K/uL
Valproic Acid	50-100 ug/mL	104 ug/mL
Alcohol (Blood)	0 mg/dL	0 mg/dL

DISCUSSION

The exact pathophysiological mechanism of hyperammonemic encephalopathy induced by the interaction between divalproex sodium and topiramate is unknown [11]. One possible mechanism suggests divalproex sodium inhibiting the first enzymatic reaction in the urea cycle, carbamoyl phosphate synthetase I, causes a rise in plasma ammonia levels [7]. The changes in mental status may be due to the increased glutamine synthetase activity which resulted from hyperammonemia [7]. The increased glutamine then causes an osmotic shift of fluid into astrocytes causing astrocytes to swell and produce cerebral edema [7]. When topiramate is added to divalproex sodium, synergistic effects are observed which causes a further increase in ammonia levels and glutamine [12]. Hyperammonemic encephalopathy can occur with or without hepatic failure [3,5]. Other symptoms of hyperammonemic encephalopathy include altered mental status, confusion, lethargy, depression or anxiety, seizures, insomnia, and changes in behavior and personality [7].

In some cases, the difficulty with hyperammonemic encephalopathy related to valproic acid and concomitant topiramate is that patients who are prescribed this combination of medications potentially have a confounding behavioral health diagnosis or a mood disorder such as bipolar disorder with or without a seizure disorder. This particular patient had a diagnosis of schizoaffective disorder and a long history of seizure beginning at two years of age, so it is likely that the patient was receiving this combination of medications to target both diagnoses. Common signs and symptoms of schizoaffective disorder include those associated with schizophrenia with a superimposed depressive state or mood disorder. Presenting symptoms such as poverty of speech or thought, confusion, incoherence, fatigue, drowsiness, or sedation can overlap and be difficult to differentiate between hyperammonemic encephalopathy and schizoaffective disorder. The clinical presentation of hyperammonemic encephalopathy can be easily misdiagnosed due to the similarities in presentation of psychiatric disorders [12] and when patients have both a psychiatric and neurologic disorder, the use of divalproex sodium is common.

It is especially important with this patient population to rule out any potential drug-induced diagnoses as well as decompensation or worsening of the known behavioral health diagnosis and evaluate the patient for potential new diagnosis or problems altogether. In this particular patient case, cirrhosis was suspected during her admission because of documentation during an inpatient stay at another facility only twelve days prior that was passed along or followed the patient to her next hospital stay. Although cirrhosis was documented as one of the patient's current problems, supporting evidence such as an INR, abdominal CT or liver biopsy were not provided. During this reported stay, cirrhosis was not pursued any further due to unremarkable liver function tests such as AST, ALT, Alk-phosphatase, and the gastrointestinal physical exam reporting no ascites, normal bowel sounds and an obese abdomen. Additionally, the patient's PMH was lacking a diagnosis or any information that could be considered an underlying cause of cirrhosis such as hepatitis, alcohol abuse, non-alcoholic fatty liver disease, or a hereditary or autoimmune cause. The interdisciplinary team felt that this evidence was sufficient for cirrhosis to be ruled out, and therefore did not pursue an abdominal CT scan or paracentesis, but the patient was referred to a GI specialist for follow-up.

This particular case is unique compared to most other case reports published in the literature for two reasons. In most cases where topiramate and divalproex sodium are being used concomitantly and patients present with elevated levels of ammonia, acute mental status changes, and drowsiness or sedation, the diagnosis of hyperammonemic encephalopathy is made early. Typically either divalproex sodium, topiramate, or both are discontinued immediately after a diagnosis or suspected hyperammonemic encephalopathy. Secondly, on presentation, this patient was already receiving both lactulose and rifaximin

at appropriate recommended doses, but still had an elevated ammonia level, confusion, and sedation. Both of these medications had been started at least twelve days prior during a four day hospital admission at another facility for similar encephalopathy symptoms. It is important to note that this patient had many hospital admissions beginning in 2012, per available records. Additionally, the patient had received both topiramate and divalproex sodium in combination since at least 2005 in different dosing strengths and/or schedule, and possibly for an even longer period of time. Previously published cases of topiramate and valproic acid induced encephalopathy report a time interval between a medication change and onset of clinical signs and symptoms ranging from 2 days to 3 years [13]. This time period is similar to the multiple records of symptomatic presentation this patient had over a three year period related to topiramate and divalproex acid changes. Twilla JD et al. presents a patient with a similar past medical history of schizoaffective disorder and seizures as the patient discussed in this case report. Both patients had comparable presentations including altered mental status, and increased somnolence, but the patient presented by Twilla JD et al. showed an EEG with moderate slowing [9]. An EEG was not performed in this patient because of unanimity among the interdisciplinary team (psychiatrist, attending physician and pharmacist) that valproic acid and topiramate were the likely culprits in this patient's symptomatology and how quickly her symptoms resolved once the offending agents were finally discontinued.

The drug interaction between divalproex sodium and topiramate causing hyperammonemic encephalopathy is noted in the package inserts for both medications. Although there is an estimated 2% incidence of hyperammonemic encephalopathy induced by the interaction between divalproex and topiramate [9], it is important to be aware this drug interaction can cause serious consequences. As seen in this patient case, this drug interaction caused the patient to experience multiple events of increased confusion and altered mental status and likely played a role in her diagnosis of cirrhosis and thus receiving medications for this that she possibly did not need. In conclusion, it is paramount to check for drug interactions, especially when polypharmacy, treatment of multiple disease states, or numerous providers are utilized.

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